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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/002,634 | 12/05/2001 | Anthony E. Bolton | 033136-226 | 1971 |

7590 07/12/2005

Gerald F. Swiss
FOLEY & LARDNER
3000 EL CAMINO REAL, SUITE 100
THREE PALO ALTO SQUARE
PALO ALTO, CA 94306-2121

| EXAMINER | |
|---|---|
| BELYAVSKYI, MICHAIL A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/002,634 | BOLTON ET AL. | |
| | Examiner | Art Unit | |
| | Michail A. Belyavskyi | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *12-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/20/05 has been entered.

Claims 12-18 are pending.

2. *Claims 12-18 drawn to a method of treatment or prophylaxis of chronic fatigue syndrome in mammalian comprising administering stressed mammalian blood cells wherein stressor is both oxidative conditions and ultraviolet radiation are under consideration in the instant application.*

In view of the amendment, filed 04/20/05 the following objection and rejections remain:

3. The disclosure stand objected to because of the following informalities: there is no Description of Figures 1 and 2 in the "Brief Description of the Drawings".

Appropriate correction is required.

Applicant's arguments, filed 04/20/05 have been fully considered, but have not been found convincing.

Applicant asserts that page 3, lines 13-15 of the Specification contain a Brief Description of the Drawings.

Contrary to Applicant's assertions, it is noted that on page 3, line 13-15 there is no description and explanation of Figures 1 and 2.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

5. Claims 12-18 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of decreasing the expression of one or more of the inflammatory cytokines IFN-γ and IL-6 from cells in mammalian patients comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation does not reasonably provide **enablement** for a method for treatment or prophylaxis chronic fatigue syndrome in a patient comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action, mailed on 02/25/05 .

Applicant's arguments, filed 04/20/05 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) a method of treatment as well as prevention are enabled by the specification and there would appear to be no basis for distinguishing between treatment and prophylaxis in terms of compliance with the enablement requirement; (ii) US Patent law never required the disclosure of studies in human to support claims drawn to the treatment of humans.

Contrary to Applicant's assertion, it is the Examiner position that Specification does not reasonably provide enablement for a method for treatment or prophylaxis of any inflammatory disease, including chronic fatigue syndrome in a patient comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation.

Moreover, in the interview with Applicant's representatives Jerald Swiss and Bill Chan on 05/26/05, the Examiner acknowledge that specification only enable for a process of decreasing the expression of one or more of the inflammatory cytokines IFN-γ and IL-6 from cells in mammalian patients comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation. Applicant agreed to consider to amend the base claim 12 to recite ' A method of decreasing the level of IL-6 in a patient".

With regards to the issue that US Patent law never required the disclosure of studies in human to support claims drawn to the treatment of humans.

It is noted that the issue raised in the previous Office Action was not about the requirement of providing studies in human to support claims drawn to the treatment of humans. It was explicitly stated that since there is no animal model studies and data in the specification to show the effectively of treatment or prophylaxis of chronic fatigue syndrome in a patient comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation it is unpredictable how to correlate a contact hypersensitivity (CHS) test on Balb/c mice and the decrease in the expression levels for cytokines IFN-γ and IL-6 in the lymph tissue of the treated animals with claimed *in vivo* use. Applicant himself acknowledge that etiology of CFS remains unknown and it is well known in the art that excessive sensitivity to IL-6 are almost certainly not the only factor controlling CFS ( see page 9, lines 20-25 in particular). In other words Applicant acknowledge that treatment and prophylaxis of CSF is subject to a number of factors which enter the picture beyond simply reduction in the levels of IL-6 by administering stressed blood cells. Since the method of treatment or prophylaxis of chronic fatigue syndrome in a patient, by administering an effective amount of stressed mammalian blood cells can be species- and model-dependent ( see Van Noort et al. International Review of Cytology, 1998, v.178, pages 127-204, Table III in particular) , it is not clear that reliance on the contact hypersensitivity (CHS) test on Balb/c mice and the decrease in the expression levels for cytokines IFN-γ and IL-6 in the lymph tissue of the treated animals accurately reflects the relative mammal and human efficacy of the claimed therapeutic strategy. The specification does not teach how to extrapolate data obtained from the above discussed studies to the development of effective *in vivo* mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of treatment or prophylaxis of chronic fatigue syndrome in a patient, by administering an effective amount of stressed mammalian blood cells. Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any pharmaceutical composition comprising stressed mammalian blood cells are fraught with uncertainties.

With regard to the issue that " there is no basis for distinguishing between treatment and prophylaxis in terms of compliance with the enablement requirement".

The Examiner disagree with Applicant's statement. The nature of the invention is such that it would require the administration of blood cells that have been extracorporeally subjected to both oxidative conditions and UV radiation that would prevent a mammalian subject from having inflammatory disease. The burden of enabling the prevention of a disease (i. e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of stressed blood cells was the agent that acted to prevent the condition. Further, the specification does not provide guidance

as to how one skilled in the art would go about screening those patients susceptible to any inflammatory disease, including chronic fatigue syndrome within the scope of the presently claimed invention. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compounds in preventing these disease states. Accordingly, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of treatment or prophylaxis of any inflammatory disease, including chronic fatigue syndrome comprising administering an effective amount of a therapeutically effective amount of of stressed mammalian blood cells in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. Also an issue was that the incorporation of essential material in the specification by reference to Kondo et al. on page 10, line 13 for a contact hypersensitivity test according to approved animal experimentation procedures is improper because an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, see MPEP 608.01(p),. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See In re Fouche, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

It is noted that Applicant has not addressed said issue.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

7. Claim 12-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/07463 or U.S. Patent No. 5,980,954 or WO00/06703 each in view of CDC Report ( 1999) for the same reason set forth in the previous Office Action, mailed on 02/25/05.

Applicant's arguments, filed 04/20/05 have been fully considered, but have not been found convincing.

Applicant asserts that : (i) one skilled in the art would not be motivated to combine the cited references; (ii) it is the association of CFS with elevated levels of IL-6 that make the method of the invention applicable to treating CFS.

Contrary to Applicant's assertion it is the Examiner position that one skilled in the art would not be motivated to combine the cited reference. It is clear that both the prior art references and applicant administered the same composition, i.e. stressed mammalian blood cells to the same patient to achieve the same results, i.e. treating inflammatory disease. The cited references are silent about the fact that disease condition in a patient is mediated by excess inflammatory cytokine production and or abnormal sensitivity of the patient to one or more inflammaroty cytokine, i.e. IL-6 . However, though applicant has proposed the mechanism by which stressed mammalian blood cells alleviates symptoms of an CFS this does not appear to distinguish the prior art teaching the same methods to achieve the same end result. Mere recognition of latent properties in the prior art does not render known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. If the prior art structure is capable of performing the intended use i.e. to treat CFS, then it meets the claim.

In the instant case, the WO ' 703 teaches a method of treating GVHD in a mammalian patient comprises administering to the patient stressed mammalian blood cells (see the entire document Abstract in particular . The WO '703 teaches that stress blood cells

have been extracting from the patient an aliquot of blood of volume, contacting the aliquot of blood, extracorporeally subject to at both oxidative conditions, ultraviolet radiation and heat stress simultaneously. ( see overlapping pages 5-6 and 7 in particular). The WO '703 teaches that oxidative environment, such as a mixture of ozone, wherein an ozone content from about 1 to about 100 μg/ml and oxygen bubbled through the blood aliquot, from about 0.5 to 60 min (pages 7 and 9 , in particular). The WO '703 teaches that the temperature stressor is in a range from about 40 to about 55° C ( see pages 8 and 11 in particular). The WO '703 teaches that UV stessor is UV-c radiation ( see page 8 in particular). Wherein the patient is human and the aliquot of modified mammalian blood is the patient's own blood , of volume from about 0.1- 500 ml (page 7, in particular).

The WO ' 436 teaches a method of treating an inflammatory disease including inflammatory bowel disease and rheumatoid arthritis in a mammalian patient comprises administering to the patient stressed mammalian blood cells (see the entire document, pages 1, 17, and 23 in particular) . The WO ' 436 teaches that stress blood cells have been extracting from the patient an aliquot of blood of volume, contacting the aliquot of blood, extracorporeally subject to at both oxidative conditions, ultraviolet radiation and heat stress simultaneously. ( see overlapping pages 13-14 and 16-17 in particular). The WO ' 436 teaches that oxidative environment, such as a mixture of ozone, wherein an ozone content from about 1.0 to about 100 μg/ml and oxygen bubbled through the blood aliquot, from about 0.5 to 60 min (pages 14-15, in particular). The WO ' 436 teaches that the temperature stressor is in a range from about 40 to about 55° C ( see page 14 in particular). The WO ' 436 teaches that UV stessor is UV-c radiation ( see page 15 in particular). Wherein the patient is human (page 8, paragraph 3 in particular), and the aliquot of modified mammalian blood is the patient's own blood (page 12, paragraph 4 in particular), of volume from about 0.01-400 ml (pages 8, 13, in particular).

The US Patent '954 teaches a method of treating an inflammatory disease including inflammatory bowel disease and rheumatoid arthritis in a mammalian patient comprises administering to the patient stressed mammalian blood cells (see the entire document, column 1, and overlapping columns 7 –8 in particular). The US Patent '954 teaches that stress blood cells have been extracting from the patient an aliquot of blood of volume, contacting the aliquot of blood, extracorporeally subject to at both oxidative conditions, ultraviolet radiation and heat stress simultaneously. ( see column 6, in particular). The US Patent '954 teaches that oxidative environment, such as a mixture of ozone, wherein an ozone content from about 0.5 to about 100 μg/ml and oxygen bubbled through the blood aliquot, from about 0.5 to 60 min (see overlapping columns 7-8 and Claim 5 in particular). US Patent' 954 teaches that the temperature stressor is in a range from about 37 to about 55° C ( see column 7 and claim 4 in particular). The US Patent '954 teaches that UV stessor is UV-c radiation ( see column 8 in particular). Wherein the patient is human, and the aliquot of modified mammalian blood is the

patient's own blood of volume from about 0.01-400 ml (column 9 and claim 2 in particular).

WO 98/07463 , U.S. Patent No. 5,980,954 or WO00/06703 do not teach treating chronic fatige syndrome.

CDC Report teaches that chronic fatige syndrome is an inflammatory disease mediated by excess inflammatory cytokine production.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of CDS Report to those of WO 98/07463 or U.S. Patent No. 5,980,954 or WO00/06703 to obtain a claimed method for treating CFS.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because chronic fatige syndrome is an inflammatory disease mediated by excess inflammatory cytokine production as taught by CDC Report and can be treated by the method for treatment of an inflammatory diseases taught by WO 98/07463 , U.S. Patent No. 5,980,954 or WO00/06703. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

Claim 15 is included because the claimed ozone content from about 0.1 to about 100 μg/ml is an obvious variation of reference ranges of 1.0-100μg/ml, taught by WO'703 and WO'436 and 05-100 μg/ml taught by US Patent '954 . Therefore, the claimed invention is an obvious variation of the reference teachings, absent a showing of unobvious differences. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

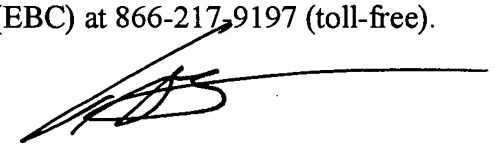
From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 571/273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Michail Belyavskyi, Ph.D.
Patent Examiner
July 11, 2005